REMARKS

1. STATUS OF THE APPLICATION

As correctly noted in the Office Action Summary, Claims 1-61 are pending. Claims 3-5 and 8-47 have been withdrawn from further consideration as being drawn to a non-elected invention. Claims 1, 2, 6, 7, and 48-51 are pending and stand rejected.

As noted in the Office Action, Applicants timely filed a Request for Continued Examination ("RCE") on November 22, 2004.

Applicants note that the Examiner acknowledged the copy of the Information Disclosure Statement submitted with the RCE on November 22, 2004.

Applicants confirmed with Examiner Angell on April 6, 2005, that the Office Action Summary should state that Claims 1, 2, 6, 7, and 48-61 stand rejected. Additionally, the Office Action Summary incorrectly indicates that Claims 1, 2, 6, 7, and 48-61 are subject to a restriction and/or election requirement; Examiner Angell confirmed that the claims are not subject to a new restriction and election requirement.

Applicants have canceled Claims 3-5 and 8-47, which were drawn to non-elected subject matter without prejudice of or disclaimer to the subject matter of the claims. Applicants reserve the right to pursue these claims in a continuation and/or divisional application.

Applicants have amended Claims 1, 2, 6, 7, and 52-61. Support for the amendment to Claim 1 is located at least in the originally filed claims, Example 3 of the specification (pp. 125-128), page 100, line 18 to page 109, line 20 and pages 115-117. Support for the amendments to Claims 2, 6, 7, and 52-61 can be found at least at in the claims as originally presented. Amendments to Claim 1 are supported at least by the claims. Applicants have amended the claims without disclaimer of or prejudice to the canceled material. Applicants reserve the right to file a continuation or divisional application on any of the subject matter canceled by way of this amendment. No prohibited new matter is believed to have been added by the entry of this paper.

Applicants have added new Claims 62-67. Support for new Claims 62-65 can be found at least in the claims as originally filed. Support for new Claims 66 and 67 is located at least in the originally filed claims, in Example 3 of the specification (pages 125-128), and page 10, lines 13-21.

All amendments are made without prejudice of or disclaimer to the cancelled subject matter. Applicants reserve the right to file a continuation or divisional application on the subject matter cancelled by way of amendment. Regarding the new claims and claim

amendments, no prohibited new subject matter is believed to have been added by entry of this amendment.

2. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 2, 52, 54-57, and 61 stand rejected as indefinite allegedly for the recitation of "the molecule." Apparently, it is unclear in these claims whether the "molecule" being referred to is one that binds to HBM or Zmax1, or is a reagent which inhibits a molecule from binding to HBM or Zmax1.

Applicants have amended Claims 1, 2, 52, 54-57, and 61 either directly or indirectly such that the term is no longer recited. The amendments to the claims thereby moot the rejection. Accordingly, Applicants respectfully request that the rejection be withdrawn.

3. REJECTION UNDER 35 U.S.C. §§ 101 AND 112, FIRST PARAGRAPH

Claims 1, 2, 6, 7, and 48-51 are rejected under 35 U.S.C. § 101, because the invention is allegedly not supported by either a credible, substantial and specific asserted utility or a well established utility.

To the extent that the rejection may apply to the claims as amended, the issues raised in the Office Action are addressed below.

3.1 The Utility Requirement

Applicants note that the Federal Circuit has stated that the threshold of utility is not high. *Juicy Whip Inc. v. Orange Bang Inc.*, 185F.3d 1364, 1366, 51 U.S.P.Q.2d 1700, 1702 (Fed. Cir. 1999) referencing *Brenner v. Manson*, 383 U.S. 519, 534 (1966). Turning to the Patent Office's comments made with regard to the "Utility Guidelines," which issued in 2001, Applicants point out the following:

> A patent examiner must accept a utility asserted by an applicant unless the Office has evidence or sound scientific reasoning to rebut the assertion. The examiner's decision ***must be supported by a preponderance of all the evidence of record.*** *In re Oetiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). More specifically when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the ***asserted utility must be accepted by the Examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion. "[A] rigorous correlation need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient."*** *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 U.S.P.Q.2d 1895, 1900 (Fed. Cir. 1996). The Office will take into account both the nature and the degree of the homology.

> When a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein. If the preponderance of the evidence of record, or of sound scientific reasoning casts doubt upon such an asserted utility, the examiner should reject the claim for lack of utility under 35 U.S.C. 101. For example, where a class of proteins is defined by common structural features, but evidence shows that the members of the class do not share a specific, substantial functional attribute or utility, despite having structural features in common, membership in the class may not impute a specific, substantial, and credible utility to a new member of the class....

66 Fed. Reg. 1096. The above text was published with the Utility Guidelines on January 5, 2001 in the Official response bye the Patent Office to Comments from the public.

Applicants assert that the Office has failed to keep in context that the threshold of utility is not high during their repeated assertion that the invention lacks utility. Additionally, the Office improperly rendered its conclusion by not applying the evidentiary standard, it takes a ***preponderance of the evidence*** to mete out a rejection based on lack of utility. The evidence presented is not such that it would lead the artisan of ordinary skill to the conclusion that there is no specific and substantial utility or that the asserted utility is not even well-established.

With reference to the Office's response to comments based on using homology to overcome an utility rejection,.it must be noted that the quoted Patent Office response relates to an example that relies ***only*** on *in silico* analysis and identification of a homology in a gene. The response does not take into account any data that shows the function of the putative gene, but rather the associated function of the gene based on its homology to another known gene. *See* Response to Comment 19, 66 Fed. Reg. 1096.

Applicants assert that the Office has taken the arguments and addressed each of the pieces of evidence in isolation of the other pieces, without viewing the arguments for what they teach ***as a whole*** in view of each other and the art at the time. The Office has not looked at what the ***preponderance of the evidence*** teaches. *See Cross v. Iizuka*, 753 F.2d 1040, 1049, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985). Even if, *arguendo*, individual lines of evidence were separately insufficient as alleged, the credibility of the asserted utility is strongly supported by the combination of the evidence ***as a whole***.

Applicants have shown that LRP5 (Zmax1) and its polymorphic variant, HBM, are members of the lipid receptor protein family. They have been shown to have a role in lipid regulation. Specifically, the Applicants provide experimental data of an altered lipid profile in

an extended kindred with the HBM phenotype (*see* Example 3, at pages 125-128). Also, the features of the Zmax1/HBM gene and its relationship with a family of receptors implicated in the ontology and physiology of atherosclerosis, arteriosclerosis, and associated related diseases and conditions are discussed. In view of the observed profiles, more than a mere allegation of homology is provided by Applicants. In rebuttal, the Office argued that lipid regulation is a complex event, such that homology is insufficient. *See* Office Action, p. 6 ("The regulation of serum lipid levels is recognized in the art as very complex...."). On page 7 of the Office Action, the Office concludes that because lipid regulation is not limited to a single process but encompasses many different processes, there is an automatic conclusion that the method for identifying molecules lacks a specific utility. Although that argument may have been persuasive if homology data was all that Applicants relied upon, it is not persuasive with the instant facts. Applicants note that the Office has itself promulgated that there is no *per se* rule on how homology data is to be assessed and each must be viewed on a case by case basis. ("There is no *per se* rule regarding homology, and each application must be judged on its own merits.") 66 Fed. Reg. 1096. Given the observed lipid profile and the post-filing articles, sufficient evidence has been presented to further support the homology data and thereby a specific and substantial utility.

The Office has not demonstrated a *prima facie* case of lack of utility. Applicants provided patient data in the specification showing that the individuals expressing the polymorphic variant, HBM, had an altered lipid profile from those individuals with the wild-type variant. In fact, the HBM affected members had a statistically significant reduction in triglyceride levels and lower VLDL levels. Specification at 127. The application also shows that Zmax1, the wild-type variant, binds to ApoE. *See* Specification, at 115. The role of ApoE at the time the application was filed and today in regulating lipids is well established. Moreover, the complexity of the system remarked upon by the Office does not negate Applicants' direct and circumstantial evidence comprising the homology of LRP5/Zmax1 to the LDLR family of receptors, the binding relationship with ApoE, and the data presented in the specification in a manner sufficient to shift the burden upon Applicants. The burden to establish a *prima facie* case rests on the Office and has not been met.

The Office also argued on rebuttal that the correlative data is not sufficient, because allegedly it did not account for differences between the lipid profiles of men and women. Office Action, p. 8 referring to the Zabaglia Abstract. Applicants point out that as quoted *supra*, only a ***reasonable correlation*** need be shown; a ***rigorous correlation*** is not required. The Office through its arguments now seems to be asserting a new utility

standard, in effect, a standard that requires a complete explanation of the working model that forms the scientific basis of the claimed invention and all related issues.

The standard that the Office now appears to be applying is improper. "[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *Newman v. Quigg*, 877 F.2d 1575, 1581, 11 U.S.P.Q.2d 1340, 1345 (Fed. Cir. 1989); *see also* 66 Fed. Reg. 1095-6. Applicants submit that the claims as amended or previously presented would have led the skilled artisan at the time to conclude, by a preponderance of the evidence, that there was a credible, substantial and specific, if not well established, utility.

3.2 The Rejection is Based on an Alleged Lack of a Substantial and Specific Utility

The Office does admit that the alleged utility is credible. Office Action, p. 5. But, the Office instead particularizes the utility issue as "not merely whether Zmax1 and *HBM* have utility in and of themselves, but whether the claimed methods of identifying *molecules involved in lipid regulation* have utility under 35 U.S.C. § 101...." Office Action, p. 5. The Office centers its argument on whether the claimed invention has a specific and substantial utility. The Office cites to a portion of M.P.E.P. § 2107.01. However, later in that very section of the M.P.E.P. entitled "Specific Utility", ***methods of screening are described as having a specific and unquestionably substantial utility***. Thus, Applicants direct the Office's attention to the Utility Guidelines of M.P.E.P. § 2107.1 entitled "Research Tools".

> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. **Many research tools such as gas chromatographs, screening assays, and nucleotide sequence techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds).** (Emphasis added).

This is not an instance of studying the characteristics of a compound or assaying for a material that itself has no specific and/or substantial utility. Here, the claims are directed to identifying molecules via an assay that bind to HBM and/or Zmax1 and thereby modulate a lipid (*e.g.*, a triglyceride or a VLDL). As discussed *supra*, and throughout Applicants' papers, based on the threshold of utility and the preponderance of Applicants' evidence, there is a specific and substantial, if not well-established, utility for the claimed methods.

3.3 Rejection for use of the Term "Involved"

Applicants note that to the extent that the rejection under 35 U.S.C. §§ 101 and 112, first paragraph relates to the recitation of the term "involved," the claims as amended no

longer recite the term. Accordingly, the rejection to the extent of the use of the term is now mooted in view of the claim amendments.

3.4 Function of and Correlation Between HBM and Zmax1

In addressing whether the claimed invention has a well-established utility, the Office questions the association of HBM with lipid regulation and Zmax1's role in lipid regulation. Office Action, pages 8-9. Zmax1 is a wild-type gene. HBM is a polymorphic variant of the Zmax1 gene. The HBM nucleic acid has a single nucleotide change that results in a one amino acid change in the protein. When expressed in humans, the HBM variant results in one phenotype being enhanced bone mass in the affected individual. Nevertheless, the genes are the same; HBM is merely an allelic variant of the wild-type. The proteins encoded by Zmax1 and HBM are involved in the same signaling cascades. The only difference being that the biological activity of the proteins in those same signaling cascades has been altered, as observed and discussed in Example 3 of the specification, as discussed *supra*. Nevertheless, the Office appears to consider HBM and Zmax1 as entirely separate genes, with different functions in different signaling cascades. They are not.

Applicants have provided data shown in Example 3 of the specification that demonstrates that the HBM variant when expressed in humans is correlated to an altered lipid profile. The tabulated data of Example 3 presents profiles for affected members having the HBM variant (marked "A") and profiles of unaffected members having Zmax1, i.e. wt-LRP5 (marked "U"). Thus, the skilled artisan could correlate the observed phenotype to a function of Zmax1 caused by the HBM polymorphism. Even though a significant correlation is clearly shown by Applicants' data, it should be recognized that a rigorous correlation need not be shown in order to establish practical utility. *Fujikawa*, 93 F.3d at 1565, 38 U.S.P.Q.2d at 1900.

3.5 Associated Rejection under 35 U.S.C. § 112, First Paragraph

On page 9 of the Office Action, the Office asserts that because there is no utility, one skilled in the art would not have known how to use the invention, thus, the combined rejection of lack of utility and lack of enablement under 35 U.S.C. § 112, first paragraph. Applicants disagree. As stated above, there is at least a credible, specific and substantial utility if not a well established utility. In view of the amended claims, one of skill in the art would have known at the time how to use the HBM and/or Zmax1 sequences to identify reagents that bind to HBM and/or Zmax1 and thereby regulate a lipid.

In view of the above arguments and the amendments to the claims, the rejection under 35 U.S.C. §§ 101 and 112, first paragraph, respectfully should be withdrawn.

4. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (WRITTEN DESCRIPTION)

Claims 1, 2, 6, 7, and 48-61 stand rejected under 35 U.S.C. § 112, first paragraph as purportedly lacking written description. Applicants traverse the rejection to the extent that it applies to the unamended claims. Applicants traverse the rejection with respect to the claims as amended or as it may apply to the unamended claims.

4.1 Written Description Requirement

There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. *In re Wertheim*, 541 F.2d 257, 263, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976) and M.P.E.P. § 2163. To satisfy the written description requirement, an application must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession it. M.P.E.P. § 2163. This must be done by identifying the claim limitation at issue and to establish a *prima facie* case by providing reasons ***why*** a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of it. M.P.E.P. §§ 2163 and 2163.04 (Emphasis added).

4.2 Size of the Genus of Molecules Identified

The Office bases an aspect of its rejection of lack of written description, because the alleged genus of molecules encompassed by the claims is large. The Office alleges that the genus "comprises an indefinite number of species molecules."

Applicants disagree. The argument to the extent it applies to the claims as amended is irrelevant. The claims are to methods of identifying compounds. What must be described is the process of identifying the compounds and not the compounds themselves. If description required identification of the compounds and characterization of those compounds, it would defeat the purpose of having the claim. The claim is for an assay in order to identify compounds which modulate a lipid. Thus, the number of potential species that potentially fall within the genus of compounds that can be identified by the assay is not pertinent to the question of whether the specification provides sufficient description for the claimed method. The specification does provide sufficient description to place the public on notice that Applicants had possession of the claimed method.

Accordingly, to the extent that the written description rejection hinged on the number of species, in view of the above argument, the rejection should respectfully be withdrawn.

4.3 Molecules that inhibit the binding of another molecule to HBM and/or Zmax1

On pages 9-10 of the Office Action, the Office appears to reject the claims, because the claims encompass reagents that inhibit binding of a ligand to HBM or Zmax1, wherein the second molecule can be any molecule that binds to HBM and/or Zmax1. Without

acquiescing as to the written description of this limitation, Applicants have amended the claims such that the claims are directed to identifying reagents which bind to HBM and/or Zmax1, and thereby regulate lipids. The issue of written description stemming from the limitation relating to the second molecule is thereby mooted. Accordingly, the rejection for lack of written description to the extent that it relies on this argument, is respectfully requested to be withdrawn.

4.4 Conditions of the Assay

The methods claimed relate to a general procedure for determining reagents that can modulate a lipid. Thus, the claim is not directed to specific conditions under which the methods are to be performed. To the extent that the rejection hinges on conditions, Applicants address the rejection with respect to the claims as amended.

The claims are directed to a genus of methods to identify compounds. The precise conditions under which each available assay method must be performed is inappropriate given the nature of the claims. The claims are directed to a genus of methods, wherein HBM and/or Zmax1 are utilized as the bait or screening reagent to determine if a specific reagent binds to HBM and/or Zmax1, and further in turn whether when said reagent is administered to an animal, whether said reagent modulates a lipid.

Thus, the skilled artisan would have understood that there is an *in vitro* aspect of determining binding by any of the known means in the art followed by a determination of whether lipid(s) levels have been regulated by the binding in an animal. Numerous *in vitro* binding assays were known at the time and were well developed such that the skilled artisan would have understood the aspect of studying binding and the conditions needed therefore. Additionally, determination of lipid modulation, whether analyzing triglyceride and/or VLDL levels or a lipid profile, also would have been understood. Analysis of lipid profiles have been well known for years.

Accordingly, in light of the amendments to the claims and the arguments asserted above, the skilled artisan would have understood that Applicants were in possession of the claimed, methods. Applicants therefore respectfully request withdrawal of the rejection.

5. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (ENABLEMENT)

Claims 1, 2, 6, 7, and 48-61 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking an enabling disclosure. Applicants traverse the rejection to the pending claims, or the claims as amended to the extent that the rejection may apply.

5.1 Enablement Requirement

In order to make a rejection, the Office has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright,* 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). Whenever a rejection for lack of enablement is made, the Office must explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and back up assertions of its own with acceptable evidence or reasoning which is consistent with the statement. *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971) and M.P.E.P. § 2154.04. The standard for setting forth a *prima facie* case of lack of enablement is the determination of whether the experimentation needed to practice the invention is undue or unreasonable.

5.2 Inhibiting a Molecule that Binds to HBM or Zmax1

Without acquiescing to the rejection and to the extent that the rejection flows from the claim limitation relating to identifying an agent that inhibits a ligand from binding to HBM and/or Zmax1 by binding to that ligand, Applicants have amended the claims such that this limitation is no longer present. Office Action, page 15 ("Working Examples and Guidance in the Specification"). Accordingly, the rejection to the extent that this limitation is at issue, is mooted by the amendment.

5.3 Effect of Binding of the Molecule to Zmax1/HBM on Lipid Regulation

On page 13 of the Office Action, the Office asserts that "the claims and specification do not indicate what effect binding of the molecule to Zmax1/HBM would have on lipid regulation. That is, it is not clear from the specification if a molecule identified in the process would be a molecule that increased lipid levels, decreased lipid levels, or even which specific lipids the molecule would effect."

Applicants traverse the rejection to the extent they apply to the amended claims. The claims are directed to a method. The method recites a method of identifying a reagent that modulates lipid. Applicants have shown that individuals expressing the HBM phenotype have an altered phenotype (*i.e.*, statistically significant reductions in triglyceride and VLDL levels). *See* Specification, at 127. It was also found in men expressing the HBM polymorphism, that there was a statistically different ratio of LDL to HDL levels. Thus, at the very least, the skilled artisan would expect that reagents screened by the claimed methods would modulate triglycerides and VLDLs. Additionally, a skilled artisan would know to look at the lipid profile of LDL to HDL of a particular reagent using the claimed assay.

Thus, to the extent that the rejection turns on this limitation, the rejection should be withdrawn in view of the arguments presented above.

5.4 Involvement of HBM/Zmax1 in Lipid Regulation and Unpredictability in the Art

On page 14 of the Office Action, the Office asserts that to identify molecules involved in lipid regulation, it is imperative that HBM and Zmax1 are specifically involved in lipid regulation. The Office admits that the disclosure describes that HBM and Zmax1 are LDL-receptor family members. However, the Examiner asserts that there is no disclosure in the specification which indicates that HBM or Zmax1 is a functional LDL receptor that is directly involved in lipid regulation. On page 15, the Office goes on to argue that LDL receptors are involved in processes other than lipid metabolism, and that although other HBM and Zmax1 are members of the LDL family of proteins, this fact is insufficient to establish that HBM/Zmax1 are directly involved in lipid regulation.

Applicants disagree and traverse the rejection as it applies to the claims as amended or as previously examined. First, as discussed above, there is a homology between Zmax1 and HBM and the LDL receptor, which indicates they are members of the LDL receptor family. Second, Zmax1 is disclosed as binding ApoE, a lipoprotein. Third, Applicants demonstrate via direct data dependent on the polymorphic variant, HBM, that there is an enhanced lipid profile, *i.e.*, a significant reduction in triglycerides and VLDLs, which are known as bad lipids. *See* Example 3.

The fact that the lipid system is complex is to be expected given the cascades and pathways involved. Zmax1/HBM is part of the Wnt pathway. Thus, the fact that HBM and Zmax1 may also be involved with pathways not involved in modulating lipid regulation, such as bone modulations, does not detract from their apparent role in the processes disclosed in the present application given the nature of the Wnt pathway. The complexity of the Wnt pathway and lipid metabolism in general does not negate the statistically significant data presented in Example 3.

Thus, to the extent that the rejection relies on this limitation, the rejection should be withdrawn.

5.5 Quantity of Experimentation

On page 17 of the Office Action, it is argued that "[i]n order to practice the claimed invention...additional experimentation would be required in order to first identify the molecules that bind to Zamx1 or HBM." And, once these molecules were identified, the Office argued that more experimentation would be required in order to determine which of the molecules had an effect on lipid regulation in a subject.

Applicants assert that the *Wands* factor of quantity of experimentation is misapplied. Applicants have amended the claims to be directed to a method of identifying agents that both bind HBM and/or Zmax1 and modulate lipids. The claims are directed to a screening

process and not to the compound identified by the method. The Office does not assert that it would take undue experimentation in order to perform the assay. Instead, the Office directs the rejection to the limitation of the reagents to be screened. Screening reagents, given the assay, would have been routine at the time, no more labor intensive or requiring greater experimentation than making and screening monoclonal antibodies and determining whether those antibodies bind the antigen of interest, which was found to be not undue in the *Wands* case. *See In re Wands,* 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1406 (Fed. Cir. 1988).

Further, regarding the lipid regulation screening step, as in *Wands*, the method can be viewed as a two-step screening process. The first step seeks to determine binding (like in *Wands* wherein the Applicants sought binding of the monoclonal antibodies to HBsAg). *Wands*, 858 F.2d at 739, 8 U.S.P.Q.2d at 1406. The second step is to determine whether the reagent can regulate lipids. In *Wands*, there was another screening step for the antibodies wherein the monoclonal antibodies were further tested for their affinity and additional screening beyond binding to HBsAg antigen. *Id.*

Accordingly, Applicants assert that the factor of quantity of experimentation has been misapplied, and when viewed appropriately, the amount of experimentation required falls well within the boundaries of what would have been reasonable for the skilled artisan to do at the time.

Thus, for at least the reasons presented above and in view of the amendments to the claims, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph for lack of an enabling disclosure.

6. RESPONSE TO ARGUMENTS

On page 18 to page 22 of the Office Action, the Office responded to Applicants arguments filed November 22, 2004. Applicants disagree with the Office's position and arguments presented on pages 18 to 22.

On page 20, the Office asserts that the references of Magoori et al. and Fujino et al. did not indicate how LRP5 is specifically involved in lipid regulation. Applicants point out that the exact model of how an invention works does not have to be disclosed, because it does not even have to be known. *See* 66 Fed. Reg. 1095-96 citing to *Newman v. Quigg,* 877 F.2d 1575, 1581, 11 U.S.P.Q.2d 1340, 1345 (Fed. Cir. 1989). Therefore, the fact that the exact model of lipid regulation is not fully elucidated is not pertinent to whether the claims have utility.

The Office also argued that the data of Magoori and Fujino did not teach that LRP5 is directly involved in lipid regulation. Applicants disagree with the Office's conclusion in view of the standard under which the evidence is to be weighed. As discussed *supra*, the

standard is a ***preponderance of the evidence***. Whether directly or indirectly, the evidence presented both in the specification and in the post-filing articles submitted both provide evidence which would have led a skilled artisan to conclude at the time and today that Zmax1 and HBM are involved in lipid regulation. Applicants also disagree with the Office's representation of the references' teachings. For example, Fujino et al. (2003 *Proc. Nat'l Acad. Sci. USA* 100: 229-234) clearly state in the second sentence of their abstract "that LRP5 is also required for normal cholesterol and glucose metabolism." Given the authors' assertion and that they would likely be considered skilled artisans, it is clear that based on their evidence LRP5 is not only involved in lipid regulation but is ***required*** for normal cholesterol, metabolism, and thus lipid regulation. The Magoori et al. manuscript furthers the findings of Fujino et al. The authors reiterate that LRP5 is required for normal cholesterol metabolism. *See Summary*. The authors go on to state that the data presented suggests that LRP5 ***mediates both apoE-dependent and apoE-independent catabolism of plasma lipid proteins***. *Id.* In the discussion section of the Magoori et al., the authors go on to explain that both LDLR and ApoE are critical in the plasma clearance of cholesterol-carrying lipoproteins, including LDL and apoE-containing IDL and chylomicron remnants.

Moreover, with respect to the Zabaglia Abstract, Applicants submit herewith a certified translation of the entire Zabaglia article. (Attached hereto as Exhibit A) The translation, when considered in full supports Applicant's position throughout this proceeding that Zabaglia, in fact, demonstrates a correlation between lipid profiles and bone mass that provides further evidence of the credibility of Applicant's asserted utility.

The goal that prompted the Zabaglia study was to identify a low cost screening method for bone mass in post-menopausal women. See, Zabaglia at Introduction. Zabaglia et al. note that Bagbozan et al. and Soo et al. had previously identified a correlation between lipid profiles and bone mass. *Id.* Although Zabaglia et al. did not achieve their goal of replacing bone density scans with lipid profiles as a diagnostic tool, Zabaglia et al. did note that high total cholesterol and correlated with low bone mass and that high HDL/LDL ratios correlated with higher bone mass. See, Zabaglia at Discussion first paragraph.

Despite failing to establish a new diagnostic, Zabaglia et al. did show a positive correlation between lipid profiles and bone mass density. See, Zabaglia at Discussion. Thus, Zabaglia provides further evidence of a common element in the mechanisms of regulating lipid metabolism and bone mass and further supports the credibility of the presently asserted utility. Further, Zabaglia studied a population limited by age and gender in contrast to the kindred studied in the present specification. Thus, the strong and

statistically significant correlation observed by Applicants, as shown in Example 3 of the specification, would be particularly impressive to one of skill in the art.

The Office appears to be selectively choosing from amongst the data of these references and combining only those aspects of data from the different references in order to manufacture support for the Office's position that there is no utility for the claimed methods. In contrast to the Offices selective citation, the references of Magoori and Fujino must be taken for what they teach as a whole and what the authors conclude. Based on the conclusions of those authors, Applicants not only have an asserted utility that is both specific and substantial, there is a well established utility.

The Office also argues on page 20, that since LRP5, Zmax1 and HBM are not identical, it is possible that they have very different functions, and thus the LRP5 data is questionable. As stated in Section 3.4 *supra*, these genes are all variants of each other. In the instance of LRP5 and Zmax1, both are considered wild-type variants. With regard to HBM, there is an amino acid substitution that has been characterized as being responsible for high bone mass in a population of people expressing the variant. The gene responsible for all three proteins is located in the same place on the human chromosome. The differences in the protein does not change the action of the protein in various signal cascades.

On page 21, third paragraph, the Office even asserts that the references of Johnson and Little do not teach that a single locus is responsible for the phenotype is the HBM gene or the Zmax1 gene. Applicants disagree. The paper by Johnson et al. (1997 *Am. J. Hum. Genet.* 60: 1326-1332) describes the history of the identification of the kindred with the gain of function mutation that was later identified in the Little et al. paper to be due to a mutation of LRP5. The authors of Little et al. clearly state that from their analysis "we identified a mutation, in the low-density lipoprotein receptor-related protein 5 gene (*LRP5*), that results in the HBM phenotype." Little et al., 2002 *Am. J. Hum. Genet.* 70: 11-19, 12. The single nucleotide transversion of G-to-T resulted in a glycine-to-valine amino acid change. All the affected individuals from the study were heterozygous for the mutation. Little et al., at 17. Little et al. go on to discuss that the mutation occurs near the fourth YWTD repeat of the first YWTD/EGF domain in LRP5. *Id.* The authors pointed out in their article that mutations in the YWTD domains of LDLRs have been shown to cause familial hypercholesterolemia. *Id.* The findings of mutations in the YWTD domains of the LDLRs being shown to cause familial hypercholesterolemia further supports the findings of Magoori et al., and Fujino et al., as discussed above.

The Office on page 21, asserts that the Ye et al. reference (2000 *Am. J. Clin. Nutr.* 72(supple): 1275S-84S) is cited only to support the Office's position that the process of lipid regulation is a complex, multi-factorial process, which supports the Office's argument that the claimed method allegedly does not have specific and substantial utility. Applicants disagree with the conclusion reached by the Office. The Office again views the teachings of Ye et al. in isolation of the other art references discussed above. Ye et al. do not negate or teach away from any of the references discussed above. Thus, the teachings of Little, Johnson, Magoori, and Fujino all are in agreement that LRP5 is involved in lipid metabolism.

On pages 21 to 22 of the Office Action, the Office refers to Willnow et al. (1999 *Nature Cell Biology* 1: E157-162) purportedly for the position that LDL receptors can be involved in functions other than lipid regulation as part of the enablement rejection. Again, Applicants assert that the application of Willnow in either the enablement rejection or as part of the utility rejection is improper. The fact that Willnow suggests that LDL receptors have a multitude of functions does not negate the data by, for example, Fujino and Magoori as well as the application, all of which show that Zmax1 and LRP5 are involved in lipid regulation. Neither Ye nor Willnow address or negate the data presented by Applicants or the data presented in Fujino and Magoori.

Thus, Applicants assert that the Office has not supported a *prima facie* case of lack of utility based on its references and/or arguments presented. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §§ 101 and 112, first paragraph.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

In the event any further fees are due to maintain pendency of this application, the Examiner is authorized to charge such fees to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL, P.C./
BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: August 23, 2005

By: _____
Christopher L. North
Registration No. 50,433

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

VA 725085.1